



PRINCIPE FELIPE  
CENTRO DE INVESTIGACION

## CIPF Seminar

### The CESAR Therapeutic strategy (Cancer's Epigenetic Short-circuit Adapted Response)

Speaker: **Octavio Romero Ferraro**

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Date: **19/07/19- 12:30h**

Place: Salón de Actos CIPF

The standard treatment for early stage non-small cell lung cancer (NSCLCs) patients is surgery whereas for advance disease the treatment is chemotherapy and, in some cases, radiotherapy. New therapeutics, such as tyrosine kinase inhibitors or immunotherapy may improve survival, but these treatments are only effective in small cohorts of patients. Thus, hopes of improving survival of lung cancer patients are related to the advent of novel therapeutic strategies. In our previous work, we identified frequent inactivating mutations (about 20%-30% in NSCLC) in the epigenetic gene BRG1, which were mutually exclusive with amplification in the MYC-family of oncogenes. Cells that lack BRG1 were refractory to the administration of glucocorticoids (GC) and retinoic acid (RA). On the other hand, BRG1-mutant cancer cells were also unable to respond to certain epigenetic therapies, alone or in combination with hormones. In contrast, cancer cells carrying MYC amplification, which are BRG1 proficient, appear to be highly sensitive to these therapeutic combinations. These results show that MYC amplification could be used as a prognostic biomarker for an epigenetic personalized therapy. We have designed a new strategy, so-called CESAR (Cancer's Epigenetic Short-circuit Adapted Response), which emerged as the rational combination of specific epigenetic inhibitors enhancing the action of appropriate stimuli (hormones and vitamins) that lead to a decreased growth or death in cancer cells, depending on the specific mutational background at the different epigenetic factors. This strategy seeks the "Achilles heel" of each cancer, since the same mutation in an epigenetic factor that confer aggressiveness to the tumor, cause weaknesses in other routes that, when attacked in a specific way, promotes the collapse and death of the tumor. Our data show that, at genetic level, inactivation of histone demethylases (KDMs) or histone methyltransferases (KMTs) tend to be mutually exclusive with inactivating mutations in the different SWI/SNF members (including BRG1) and with amplification of MYC-family of oncogenes. These inactivating mutations of epigenetic factors can be exploited as molecular switches that when "switched off" cause an epigenetic short circuit, leaving the tumor vulnerable to specific treatment against other molecules of the same epigenetic network. Our results also show that a proficient BRG1 is necessary to KDMs and KMTs expression and regulation in the vast majority of human cancer types, including lung, ovarian, breast, and pancreatic cancer, among others. This, together with the mutually exclusive inactivating mutations, implicates a new synthetic lethality in cancer. In this project we determined how inactivating mutations in BRG1 sensitize cancer cells to specific KDM/KMT inhibitors affecting cell viability.

For this propose we have integrated state of the art technology like genome-wide chromatin modification and transcriptome analysis, using different models for human cancer such as cancer cell lines and an in vivo preclinical mice models like PDXs (Patient derived orthotopically implanted xenografts). The results obtained in this study will be of great value for the stratification of tumors according to their genetic or epigenetic background for tailored treatments.

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